REMARKS

Applicant has amended claim 1 to make explicit that which was implicit, namely that the mutation scanning array contains at least 10 genes, which are used to detect within a target DNA whether any of the genes present on the array are also present in the target DNA and contain a mutation(s). Similarly, claims 3, 4, 5, 6, 9, and 10, which depend on claim 1, have been amended to make explicit which genes are referred to. These amendments are supported throughout the specification, for example at page 3, paragraph 7 and page 9, paragraph 29. As such, these amendments do not introduce new matter and their entry is respectfully requested. Claim 16 has been amended to make explicit that which was implicit, and does not introduce new matter. New claims 17 – 25 mirror claims 2 – 10 but depend upon allowed claim 12. These claims are supported by original claims 2 – 10, and do not introduce new matter. Their entry is respectfully requested.

The Applicant greatly appreciates the Examiner's allowance of claims 12 and 13, and the indication that claim 16 is free of prior art. Applicant also appreciates the withdrawal of previously cited references, including Wodicka and Beutler.

By the present amendment, Applicant has added new claims 17 – 25 which depend on claim 12. These claims make explicit certain preferred embodiments of allowed claim 12. As such, Applicant believes these claims do not introduce new matter, and their entry is respectfully requested.

Applicant has amended the specification to introduce the priority language to claim benefit of prior applications. As such, this amendment does not introduce new matter and its entry is respectfully requested. Applicant also notes that the original continuation application,

filed May 15, 2001, contained a request to amend the specification in the "relate back" section of the new application transmittal.

Claims 1 – 11 and 16 were rejected under 35 U.S.C. § 112, second paragraph.

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

Applicant has amended the claims to make explicit what was implicit. The present invention is directed to the use of DNA technology to detect mutations in at least 10 different genes, by scanning those genes at the same time. In this method, the array contains immobilized oligonucleotides which collectively span a number of genes. The number of array genes may be as small as 10 genes, or it may represent hundreds or thousands of genes, such as an entire genome. To determine whether a target DNA contains any mutations in any of the array genes, the target DNA is first hybridized to a control, wild-type DNA. The method teaches how to hybridize the target DNA to the control DNA to create a duplex. If there is a mutation in a target gene relative to the control, a mismatch is formed. The method then teaches how to isolate duplexes which contain such mismatches, and how to use the array to identify the mutated target gene, by determining which array gene it corresponds to. This method has many applications, as taught by the specification. For example, there is increasing recognition that in many disorders there is a set of genes is associated with the disorder. Thus, it is valuable to characterize (or profile) whether there are mutations in any of that set of disorder genes in an individual, rather than just looking at a single gene associated with the disorder. Thus, the method of the present invention is particularly useful for characterizing such disease gene profiles.

Applicant sumbits that in the present invention, the genes that are being scanned are those genes that are on the array itself. The Examiner has indicated at page 10, lines 13-15, that

the claims do not have a step that requires 10 different genes to be examined. However, the genes that are being examined are those genes that are on the array itself. The method allows one to ask in a certain target DNA whether there are mutations in any of the genes which are represented on the array; thus, it is the array genes which are being analyzed.

The claims have now been amended to make the invention more explicit. More specifically, claim 1 has been amended to explicitly indicate that array itself comprises at least 10 genes to analyze in the target DNA. Claim 1 has also been amended to make explicit that the array genes are all examined at the same time. Claims 2 – 6 and 9 – 10 have also been amended to make it clear that these claims are directed to the array genes. For example, in the method of claim 6, a set of genes which are known to be associated with a disorder, such as lung cancer, can be placed on the array and used to analyze a target DNA which is the total DNA from a smoker, to determine whether the smoker has mutations in any of the genes known to be associated with lung cancer.

Applicant respectfully submits that these amendments to the claims have obviated the rejection, for the following reasons. Claim 1 has been amended to provide an antecedent basis for "genomic genes." Claim 1 and its dependent claims 3, 4, 5, 6, 9, and 10 have been amended to clearly indicate that the genes which are the subject of each of those claims are the genes represented by the oligonucleotides of the array, and are referred to as the array genes. Claim 16 has been amended to make explicit that the each target gene is a contiguous gene

Accordingly, applicant respectfully submits that all rejections of the claims under 35 U.S.C. § 112, second paragraph should be withdrawn.

Claims 1, 2, 3, 4, 5 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Modrich (U.S. 5,459,039) in view of Chee (Science 274:610-614 (1996)).

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

As acknowledged by the Examiner, the primary reference being relied upon in this rejection, Modrich, fundamentally does not teach a critical feature of the present invention: the use of a mutation scanning array with a population of array genes to detect unknown mutations in a target sample of DNA. Previous technology to scan for polymorphisms and mutations was restricted to looking at mutations in a single specific gene, and does not teach or suggest how to detect unknown mutations in a population of many genes.

The Examiner has stated that the Modrich method "differs from the claimed method only in that the methodology used to identify the gene and gene segment to which the selected mismatch belongs is different" (page 6 of June 21, 2004 Office Action, lines 5-6; emphasis added). However, this "only" difference is in fact key to the Applicant's invention, because it is precisely this detection methodology which allows the present invention to scan many genes at once. As described above, this permits the artisan to understand and/or discover relationships between multiple genes and different disorders or infections, by simultaneously looking at a set of disorder genes for mutations.

In contrast, Modrich begins with a single known gene, rather than a population of multiple genes, and looks for the presence of any mutations in that gene. Although the Examiner acknowledges that Modrich does not take advantage of DNA array technology, it is argued that the secondary reference, Chee, provides this aspect of the claimed invention, namely, to apply the method of Modrich to a DNA array to detect mutations in multiple genes simultaneously. However, this position completely ignores a fundamental defect in Modrich, which is the complete failure to teach the desirability of using its mutation detection method to scan multiple

genes. Without such a teaching, there is a complete lack of motivation to combine the references except by impermissible hindsight.

A fundamental difference between Chee and the present invention is that Chee is concerned with improved methods for constructing DNA arrays, and in no way teaches or suggests the use of creating heteroduplexed DNA, and tagging mismatches with a detectable moiety, for the detection of mutations. Although the Examiner has contended that Chee allegedly teaches identification of mutations, nothing in Chee suggests the mismatch detection methods of the present invention, namely the isolation of mismatches in duplex DNA followed by detection on the mutation scanning array. Thus, Chee does not provide any suggestion or motivation to use tagging mismatched basepairs in duplexed DNA to isolate mutations, prior to the use of an array. Thus, there is no reason to combine the references based upon either reference.

The Examiner has contended with respect to claim 2 that in Chee, "segments could be amplified and then tagged" (see page 6 of the Office Action; emphasis added). The Examiner has made similar arguments regarding claims 3, 4, 5, and 11. However, Applicant respectfully submits that the Examiner is again using impermissible hindsight reconstruction to provide the motivation to combine isolated methods, where such motivation simply was not given. Hybridization of nucleic acid was known in the art, just as amplification and labeling of nucleic acids was known. However, the present invention provides an entirely novel combination of such techniques to create a novel method to solve a specific problem namely, detection of multiple mutations in a target DNA.

Accordingly, the present invention adopts an entirely different approach from the prior art and permits one to look at complex targets comprising multiple genes for the presence of any mutations.

The Examiner has also taken the position that the motivation to combine the teachings of Modrich with the teachings of Chee could be supplied by an entirely third reference, Brown (U.S. 5,376,526). Applicant respectfully disagrees that such motivation to combine these entirely separate references is supplied by Brown. As acknowledged by the Examiner, Brown is directed to a method similar to that of Modrich. However, this addition in no way cures the underlying defect in the combination of Modrich and Chee, for all of the reasons stated above. Accordingly, the combination of references does not render the present invention obvious.

Claims 6 – 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Modrich in view of Chee, and optionally in view of Brown as applied to claims 1-5 and 11, and further in view of Cronin (WO 98/30883).

Applicant respectfully disagrees for the following reasons.

All that Cronin teaches is that mutations can be searched for and identified in reference sequences, including genes for specific disease conditions. However, for all of the reasons stated above, this addition does nothing to cure the fundamental defect in the combination of Modrich and Chee, and/or Brown, which do not teach a mutation scanning array when read together. Accordingly, this combination of references does not render the present invention obvious.

Accordingly, applicant respectfully submits that the claims comply with 35 U.S.C. §103(a) and that this rejection of the claims should be withdrawn.

In view of the foregoing, applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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Ronald I. Eisenstein, Reg. No. 30,628
Nicole L. M. Valtz, Reg. No. 47,150
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110
617.345.6054